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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/416,735	10/13/99	ATENCIO I	CJ-08970

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/416,735	Applicant(s) Atencio
	Examiner Anne-Marie Baker	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Nov 27, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *5-7 and 17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *5-7 and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed on November 27, 2000 (Paper No. 4) has been entered. Applicants' election without traverse of Group III, Claims 5-7 and 17 is acknowledged. Claims 1-4, 8-16, and 18-20 have been cancelled. The elected invention is drawn to a method of increasing the infectivity of a cell to a viral vector by treatment of the cell with a calpain inhibitor.

Claims 5-7 and 17 are examined herein.

Double Patenting

Applicant is advised that should Claim 7 be found allowable, Claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the two claims are identical in wording.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-7 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of increasing the infectivity of a cell to a viral vector by treatment of the cell with a micro-calpain inhibitor, does not reasonably provide enablement for an *in vivo* or *in vitro* method

of increasing the infectivity of a cell to a viral vector by treatment of the cell with any inhibitor of any calpain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for increasing the infectivity of a cell to a viral vector by treatment of the cell with a calpain inhibitor. The claims encompass both *in vitro* and *in vivo* applications of the method.

As a first issue, the specification fails to provide an enabling disclosure for the use of **any inhibitor of any calpain** in a method for increasing the infectivity of a cell to a viral vector by treatment of the cell with the inhibitor. The specification is enabling for the use of a **micro-calpain inhibitor only**. The specification teaches only one inhibitor, calpain inhibitor 1 (*n*-acetyl-leu-leu-norleucinal), that functions in the manner intended. The specification does not teach other inhibitors that function in the manner recited in the claims. The Examiner agrees that micro-calpain inhibitors increase the infectivity of a target cell to a viral vector, *in vitro*. However, the specification is not enabling for the use of any inhibitor of any calpain for the following reasons. When the scope of the claimed method encompasses using any inhibitor of any calpain in combination with any viral vector and any target cell, as it does here, there is not sufficient guidance provided in the specification for carrying out the claimed method over the full scope. The specification is not enabling for the use of any inhibitor of any calpain to increase the *in vitro* infectivity of any viral vector for any target cell because the art teaches that some calpains are ubiquitous, while others are tissue-specific (see Gonen et al., 1997, page 17, column 2, paragraph 2). Thus, the tropism of the viral vector is critical to the operability of the invention when the invention encompasses calpains that are tissue-specific. For example, Hodgson (1995) teaches that retroviral vectors infect only dividing cells (p. 460, column 2, paragraph 4). Thus, the skilled artisan would not know how to use calpain inhibitors, other than **micro-calpain inhibitors**, in

conjunction with retroviral vectors. There is no evidence to suggest that the use of any calpain inhibitor would increase the infectivity of a target cell to a retroviral vector. There is no guidance provided in the specification to teach the skilled artisan how to determine which other calpain inhibitors could be used to increase the *in vitro* infectivity of a target cell to a retroviral vector. Thus, the scope of enablement encompasses only the use of **micro-calpain inhibitors**. Since the art teaches that micro-calpain is ubiquitous to all cell types, the skilled artisan would expect that any micro-calpain inhibitor could be used to increase the *in vitro* infectivity of any target cell to any viral vector. However, the specification is not enabling for the use of **any inhibitor of any calpain** to increase the *in vitro* infectivity of any target cell to any viral vector. For example, the skilled artisan would not know which calpain inhibitors could be used, other than micro-calpain inhibitors, to increase the infectivity of a target cell to a retroviral vector. Nor would the skilled artisan know which calpain inhibitors could be used, other than micro-calpain inhibitors, to increase the infectivity of a target cell to an adenoviral vector. There is no evidence to suggest that other calpain inhibitors would have the same effect. Given that the specification does not offer sufficient guidance to teach the skilled artisan how to practice the claimed invention over the full scope and further given that the specification discloses the effect of only a single inhibitor of micro-calpain, undue experimentation would have been required for the skilled artisan to determine which calpain inhibitors, other than micro-calpain inhibitors, could be used to produce the desired effect over the scope of any and all target cells and any and all viral vectors.

As a second issue, the specification fails to provide an enabling disclosure for *in vivo* applications of the claimed method. Further, as indicated above, the scope of enablement for *in vitro* applications of the claimed method is limited to the use of micro-calpain inhibitors.

The claimed method is an adjunct to gene therapy. Gene therapy and adjuncts to gene therapy are not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with

specific guidance. However, the specification is not enabling for *in vivo* applications of the claimed method. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH *ad hoc* committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). Given that gene therapy is itself unpredictable and not routinely successful, adjuncts to gene therapy similarly produce an unpredictable effect. Thus, absent any showing that the claimed methods are capable of producing the intended effect *in vivo*, the claims directed to an *in vivo* method for increasing the infectivity of a cell are not enabled by the disclosure.

The *in vivo* working example disclosed at pages 28-29 of the specification and in Figures 12A, B, and C, do not demonstrate an increase in infectivity of a cell upon administration of CI-1 and a viral vector. The Examiner would first like to point out that Figures 12A, B, and C include the designation "ANCB" for several of the experiments. ANCB is not defined anywhere in the specification. By day 11 post-treatment, ANCB+CI-1 had a strong effect on limiting tumor growth (Figure 12C). Since ANCB is undefined, these results cannot be interpreted. There is no evidence that administration of a calpain inhibitor in conjunction

with a viral vector, increased the **infectivity** of the target cells *in vivo*. The data only show that CI-1 has an effect on limiting tumor growth, whether administered alone or in combination with a p53-encoding viral vector. The specification states at lines 26-27 on page 28 that "calpain inhibitor alone provided significant antitumor effects." No assays were performed to determine the **infectivity** of the cells in the presence and absence of CI-1. The *in vivo* studies demonstrate enhanced cell death in the presence of CI-1, rather than increased infectivity.

Furthermore, it is useful to note that Atencio et al. (2000) disclose that "[b]ecause calpain inhibitors have been used in a variety of pathological indications to protect cells from death ..., we believe the enhancement of cell death observed in this study may be specific for tumor cells" (p. 251, column 2, paragraph 3). Again, the *in vivo* studies demonstrate enhanced cell death, not increased infectivity, and this effect may be limited to tumor cells, not broadly applicable to any cell type. Since CI-1 alone has a clear effect on limiting tumor cell growth, in a p53 mutant tumor, and the administration of rAD-p53 also limits tumor cell growth, the effect of co-administering viral vector and CI-1 can be explained by their expected combined effect, rather than by an increase in **infectivity** of the cells due to the activity of the inhibitor. Since the administration of CI-1 alone produces the desired effect of limiting tumor growth, this effect is obviously independent of any alleged increase in infectivity of the cells.

Given the lack of guidance in the specification for practicing the claimed invention *in vivo*, and further given the broad scope of the claims, the state of the art, and the unpredictability of adjuncts to gene therapy, the skilled artisan would have been required to engage in undue experimentation to practice the claimed invention *in vivo*.

Prior Art

The claims are free of the prior art because the prior art does not disclose or reasonably suggest using a calpain inhibitor to increase the infectivity of a target cell to a viral vector.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER